REMARKS

Upon entry of the amendments, set forth above, Claims 1-3 and 5-12, 14-25, 27-41, and 43-45 are pending in the present application. Claims 13, 26 and 42 have been cancelled without prejudice. Claims 1, 7, 11, 14, 21, 23-24, 27, 30, 34, 38, 43 and 44 have been amended. New Claim 46 has been added as set forth above. Accordingly, Applicants respectfully submit that the application is now in condition for allowance.

Support for the amendments can be found throughout the specification and in the claims as originally. Accordingly, no new matter has been added to the application by entering this amendment.

Pursuant to the USPTO Revised Format for Amendments, the amendments to the claims are shown by ~~strikethrough~~ for deleted matter and underlining for added matter. No accompanying "clean" version has been supplied.

Discussion of Claim Objections Under 37 C.F.R. § 1.75(c)

Claims 13, 26 and 42 were objected to under 37 C.F.R. § 1.75(c) as being improper dependent claims for failing to further limit the subject matter of the claims from which they depend. As set forth above, each of these claims has been cancelled, and therefore, the objections are moot.

Discussion of Rejection Under 35 U.S.C. § 112, Second Paragraph: Indefiniteness

Claims 1-3, 5-9, 11, 14, 21-29, 32, and 38-45 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 1

The Office Action alleged that Claim 1 was indefinite because it is not clear whether the preamble and the last method step are in agreement. As set forth above, Claim 1 has been amended to clarify that the preamble and the method are in agreement.

Claim 7

The Office Action alleged that Claim 7 was indefinite over the recitation of "wherein said PCR amplifying step comprises the addition of a binding moiety" because it is not clear to where the moiety is added. Claim 7 has been amended as set forth above to recite that the binding moiety is added to the third DNA fragment.

Claim 11

The Office Action alleged that Claim 11 was indefinite over the recitation of "specifically complementary." As set forth above, Claim 11 has been amended to remove the word "specifically."

Claim 21

The Office Action alleged that Claim 21 was indefinite over the recitation of "a product nucleic acid fragment that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence." The Office Action asserted that the third and fourth nucleic acid fragments comprise a region that confers function, and that therefore the most the final product can have is two functional regions. Nothing in the claim language requires that any fragment have only one functional region. Therefore, the basis for the rejection is unsound. Consistent with that, Claim 21 has been amended as set forth above to recite that one or both of the third and forth fragments further comprise at least one nucleic acid region that confers function. Thus, the product nucleic acid fragment can comprise one or more functional nucleic acid regions.

Claim 23

The Office Action alleged that Claim 23 was indefinite over the recitation of "said functional nucleic acid fragment" due to a lack of antecedent basis. Claim 23 has been amended as set forth above to recite "said product nucleic acid fragment," which has antecedent basis in Claim 21.

Claim 24

The Office Action alleged that Claim 24 was indefinite over the recitation of "a set of primers comprising one or more nuclease resistant, binding moieties." Claim 24 has been amended as set forth above to specify that at least one primer comprises a nuclease resistant binding moiety.

Claim 34

The Office Action alleged that Claim 34 was indefinite over the recitation of "nucleic acid fragments comprise a promoter and/or terminator" because it was not clear to the Office whether the promoter was present on one fragment and the terminator on another. Claim 34 has been amended as set forth above to recite that the 5' biological function conferring nucleic acid fragment comprises a promoter, and new Claim 46 has been added and recites that the 3' biological function conferring nucleic acid fragment comprises a terminator.

Claim 38

The Office Action alleged that Claim 38 was indefinite over the recitation of "one of the target sequences linked to at least one transcriptionally-functional region." Respectfully, the claim is clear and definite in its recitation of "at least one." In some embodiments only one transcriptionally-functional region may be linked to a target sequence by the method, for example, only a promoter, but no terminator, and *visa versa*. In other embodiments, both a promoter and a terminator, for example, may be linked by the method. At a minimum at least one such transcriptionally-functional region is added by the method. Thus, Claim 38 as originally added is clear and definite.

Claim 44

The Office Action alleged that Claim 44 was indefinite over the recitation of "functional nucleic acid molecule" in the preamble because such phrase is not defined. As set forth above, the preamble has been broadened by removing reference to "functional."

Claim 44 was also alleged to be indefinite due to recitation of "a nucleic acid molecule that comprises one or more functional nucleic acid regions joined to the polynucleotide target sequence" in step four. Allegedly, this is because in step three the third and fourth nucleic acid

fragments are added to the reaction, and either one or both comprise a region that confers function. Thus, the Action states that at most the final product can have only two functional nucleic acid regions. However, nothing in the claim language requires that any fragment have only one functional region. Thus, it is respectfully submitted that the basis for the rejection is unsound with regard to the claim as filed, and that the claim is clear and definite.

Claims 5, 14, 27, 32 and 43

The Office Action alleged that Claims 5, 14, 27, 32 and 43 were indefinite over the recitation of "a non blunt end polymerase" because it was not clear whether the phrase refers to lack of blunt ends in the target, primers, or a product of the polymerase reaction. "Non blunt end" polymerase refers to the resulting product of the polymerase reaction, meaning that the resulting product does not have blunt ends. While it is believed that this interpretation of the claims should be apparent from the specification, this clarification in the file history will remove any ambiguity. It is appropriate to consult the file history in the course of interpreting claims. *See McGill Inc. v. John Zink Co.*, 736 F.2d 666, 673-75 (Fed Cir. 1984) and *Loctite Corp. v. Ultrasea Ltd.*, 781 F.2d 861, 867 (Fed Cir. 1985).

In view of the comments and amendments set forth above, Applicants respectfully request reconsideration and withdrawal of the § 112, second paragraph rejections for lack of indefiniteness because all of the claims are clear and definite.

Discussion of Rejection Under 35 U.S.C. § 102

The Examiner has rejected Claims 1, 2, 5, 6, 10, 11, 12-16, 21, 22, 26-29 and 30-34 under 35 U.S.C. § 102 as being anticipated.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Cassata et al. (Gene, vol 212, pp. 127-135, May 1998)

The Examiner has rejected Claims 10, 11, 13 and 16 under 35 U.S.C. § 102(a) as being anticipated by Cassata et al. (referred to hereafter as "Cassata"). According to the Office Action Cassata discloses the construction of a promoter-gfp reporter gene that can be used to fuse any promoter sequence to any gene or its fragment.

Respectfully, Cassata does not anticipate independent Claim 10, or Claims 11, 13 and 16 depending therefrom, because Cassata does not teach each and every element of Claim 10. Specifically, Cassata does not disclose a method comprising PCR amplifying the second nucleic acid fragment with the third nucleic acid fragment to form a fourth nucleic acid fragment that comprises the nucleic acid sequence that confers function joined to the polynucleotide target sequence.

Cassata refers to a "second Fill-in PCR" reaction on page 128, last paragraph. The "Fill-in PCR" reaction is merely an extension reaction in which the two fragments hybridize over part of their lengths, followed by a fill-in or extension reaction to complete the joined fragments. However, the extended fragments are not amplified by PCR. Therefore, Claim 10 is not anticipated because Cassata does not disclose PCR amplification as set forth therein.

Prodromou et al. (Protein Engineering, vol. 5, pp. 827-829 (1992))

The Examiner has rejected Claims 1, 2, 10, 12-15, 21, 22, 26-29 and 30-34 under 35 U.S.C. § 102(b) as being anticipated by Prodromou et al. (referred to hereafter as "Prodromou"). According to the Office Action, the recursive PCR method disclosed by Prodromou anticipates the above-mentioned claims.

Respectfully, Prodromou does not teach each and every element of the independent claims. Prodromou, a 1992 reference, claimed to disclose a cost and labor saving PCR technique that potentially could be used to synthesize and assemble significantly larger nucleic acids. *See* page 827, paragraph 1. Prodromou sought to assemble synthetic DNA fragments using PCR enzymes. *See id.* The so-called recursive PCR technique included the synthesis of 10 overlapping oligonucleotide fragments of a synthetic lysozyme sequence. *See id.* at Figs. 1-2 and page 828, paragraph 1. The synthetic fragments ranged in size from 54-86 base pairs and overlapped each other by 17-20 base pairs. *See id.* at page 828 paragraph 1. The synthetic

fragments were also modified to include 14 unique restriction sites for subsequent subcloning and mutagenesis. *See id.* These synthetic fragments assembled together by PCR are not target nucleic acid sequences as recited in rejected independent Claims 1, 10, 21, and 30.

The instant claimed methods and systems are not anticipated by the methods of generating and assembling synthetic nucleic acid fragments as disclosed in Prodromou. Here, the claimed methods and system of Claims 1, 10, 21 and 30, respectively, can be used to PCR amplify target nucleic acid sequences. The synthetic fragments of Prodromou are not target nucleic acid sequences as recited by rejected Claims 1, 10, 21 and 30, but are instead pre-selected, modified synthetic oligonucleotides.

While Prodromou was interested in synthesizing sequences that were considered large at the time of its publication, the instant claimed methods and system overcome the inefficiencies previously associated with screening and identifying potentially interesting target sequences and genes from microorganisms, genomes, and cDNA libraries, for example. *See, for example,* Specification at page 1, line 18 to page 2, line 7; and page 3, line 28 to page 4, line 15; and page 8, lines 19-25. The instant claims provide simple and rapid methods for the amplification of such target sequences, for example sequences from microorganisms, genomes, and cDNA libraries. The method of assembling synthetic oligonucleotides as disclosed in Prodromou does not anticipate the instantly claimed methods and system which comprise, *inter alia*, target nucleic acid sequences.

Thus, Prodromou does not teach or disclose each and every element of independent Claims 1, 10, 21 and 30 because Prodromou does not disclose methods and systems that comprise target sequences as recited in the rejected claims.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102, and allowance of the pending application.

Discussion of Rejection Under 35 U.S.C. § 103

The Examiner rejected Claims 3, 7-9, 17-20, 23-25, 35-45 under 35 U.S.C. § 103(a) as being unpatentable over Prodromou combined with various other references. Specifically, the Office Action rejects Claims 3, 20, 23 and 35 over Prodromou in view of Felgner et al. (referred to hereafter as "Felgner") (U.S. Patent No. 6,165,720). Claims 7-8, 17-18, 24-25 and 36-37 were

rejected over Prodromou in view of Uhlman et al. (referred to hereafter as "Uhlman") (U.S. Patent No. 6,063,571). Also, Claims 7, 9, 17 and 19 were rejected over Prodromou in view of Goodchild (Bioconjugate Chemistry, vol. 1, pp. 165-187, 1990). Furthermore, Claims 38-43 were rejected over Prodromou and Mullis et al. (referred to hereafter as "Mullis") (U.S. Patent No. 4,965,188). Finally, Claims 44 and 45 were rejected over Prodromou and Uhlman.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The motivation to combine references must come from the references themselves and not from the invention. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). The case law "makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine the prior art references." *Echolochem, Inc. v Southern California Edison Co.*, 227 F.3d 1361, 1371 (Fed Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)).

Respectfully, none of the cited combinations teach or suggest all of the claim limitations, nor is there any motivation to combine absent hindsight. Therefore, none of the claims are obvious over the cited combinations of references.

Prodromou and Felgner

As mentioned above, the Office Action rejected Claims 3, 20, 23 and 35 over Prodromou in view of Felgner. Claims 3 and 20 depend from independent Claim 1, Claim 23 from independent Claim 21, and Claim 35 from independent Claim 30. Prodromou does not teach each and every element of those independent claims for the reasons set forth above. Specifically, for example, Prodromou does not disclose methods and systems that comprise target sequence amplification. Instead, Prodromou assembled synthetic nucleic acid fragments using PCR. Felgner disclosed chemical modification of DNA using peptide nucleic acids (PNAs). Thus, Felgner also does not disclose methods or systems comprising target nucleic acids, and therefore, the combination of Prodromou and Felgner fail to teach or suggest all of the claim elements.

Prodromou and Uhlman

Claims 7-8, 17-18, 24-25 and 36-37 were rejected over Prodromou and Uhlman. All of the claims respectively depend from independent claims 1, 21, or 30. As discussed above, Prodromou does not teach each and every element of those independent claims, specifically for example, Prodromou fails to disclose methods and systems that comprise target sequence amplification. Uhlman disclosed a process for amplifying nucleic acids using DNA/PNA primers. Thus, Uhlman also does not disclose methods or systems comprising target nucleic acids, and therefore, the combination of Prodromou and Uhlman fail to teach or suggest all of the claim elements.

Also, Claims 44 and 45 were rejected over Prodromou and Uhlman. Claim 44 recites methods comprising PCR amplifying, *inter alia*, a polynucleotide target sequence. For reasons similar to those discussed above, neither Prodromou or Uhlman, alone or combined teach or suggest such methods.

Prodromou and Goodchild

Claims 7, 9, 17 and 19, all of which depend from amended Claim 1, were rejected over Prodromou and Goodchild. Prodromou does not disclose each and every element of Claim 1, as already discussed. Goodchild discloses a review of the synthesis and properties of conjugates of oligonucleotides and modified oligonucleotides. Therefore, Goodchild also does not teach or suggest, for example, methods comprising PCR amplifying a target fragment of DNA.

No Suggestion or Motivation to Combine the Prodromou with the Felgner, Uhlman or Goodchild

Furthermore, only with hindsight motivation based upon the claims are the combinations of Prodromou with each of Felgner, Uhlman or Goodchild made. Prodromou recognized the difficulty in the early 1990s of synthesizing genes, even small genes, and provided a methodology for overcoming that difficulty. Felgner, Uhlman and Goodchild all relate to PNA technology. Thus, the references are directed to different objectives and provided no suggestion or motivation to combine absent hindsight.

Prodromou in view of Mullis

The Office Action rejects Claims 38-43 as being unpatentable over Prodromou and Mullis. Neither Prodromou or Mullis, alone or combined, discloses a method for creating transcriptionally-active nucleic acid sequences from a plurality of different target polypeptide-encoding DNA sequences. As discussed above, Prodromou does not disclose methods comprising PCR amplifying of target sequences. Prodromou discloses the assembly by PCR of a synthetic nucleic acid sequence. Mullis discloses general PCR methods, and thus has nothing to add to the recursive PCR methodology of Prodromou. Mullis does not disclose the claimed method comprising a plurality of target polypeptide-encoding DNA sequences. Therefore, the references alone or combined do not teach or suggest all of the limitation of independent Claim 38 and the claims depending therefrom.

Furthermore, there is no suggestion or motivation to combine the references absent illicit hindsight reconstruction. Prodromou assembled synthetic oligonucleotides using PCR, and thus disclosed no target polypeptide. It is illogical to combine such a reference with Mullis, a patent covering the general concept of PCR, to achieve the claimed method, absent hindsight. For these reasons no motivation to combine exists in the references.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

Discussion of Double Patenting Rejection

Claims 1-2, 7-8, 10-11, 16 and 21 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 4, 6, 7, 10 and 12 of U.S. Patent No. 6,280,977 (the '977 patent). Submitted herewith is a terminal disclaimer.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped

issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: August 20, 2003

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